

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benylin Non-Drowsy Dry Coughs, Syrup
Dextromethorphan hydrobromide 7.5mg/5ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Benylin Non-Drowsy for Dry Coughs contains dextromethorphan hydrobromide 7.5 mg in each 5 ml.
Excipients: Each 5ml of Benylin Non-Drowsy for Dry Coughs also contains:

Sorbitol solution	70%	E420	325	mg
Sucrose			1625	mg
Glucose			2380	mg
Sodium			4.4	mg
Ethanol	96% v/v		0.311	ml

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Syrup
A clear amber coloured syrup with a characteristic smell of peaches.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Benylin Non Drowsy for Dry Coughs is indicated for the relief of non-productive irritating cough.

4.2 Posology and method of administration

Adults and children 12 years and over:

Oral 15 mg (10 ml syrup) 3-4 times a day.
Maximum daily dose: 40 ml syrup.

Children under 12 years:

Benylin Non Drowsy for Dry Cough is not recommended (see section 4.3).

4.3 Contraindications

Known hypersensitivity to the active constituent. Concurrent use with monoamine oxidase inhibitors (MAOIs), or within 14 days after such treatment (see section 4.5).

Benylin Non Drowsy for Dry Cough is contraindicated for children for use in children under 12 years of age.

4.4 Special warnings and precautions for use

Use with caution in patients with hepatic dysfunction.

Benylin Non Drowsy for Dry Coughs should only be used under medical supervisions for persistent or chronic cough such as occurs with smoking, asthma or emphysema, or where cough is accompanied by excessive secretions.

Cases of dextromethorphan abuse have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances.

Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor metabolisers of CYP2D6. Poor metabolisers and patients with concomitant use of CYP2D6 inhibitors may experience exaggerated and/or prolonged effects of dextromethorphan. Caution should therefore be exercised in patients who are slow metabolizers of CYP2D6 or use CYP2D6 inhibitors (see also section 4.5).

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this product.

If symptoms persist, please consult your doctor.

Patients who are taking other medication and / or under the care of a physician, should consult their doctor / pharmacist before taking this product.

Do not exceed the recommended dose schedule

4.5 Interaction with other medicinal products and other forms of interaction

Dextromethorphan should not be used concurrently in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with MAOIs as there is a risk of serotonin syndrome.

CYP2D6 inhibitors

Dextromethorphan is metabolized by CYP2D6 and has an extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the dextromethorphan concentrations in the body to levels multifold higher than normal. This increases the patient's risk for toxic effects of dextromethorphan (agitation, confusion, tremor, insomnia, diarrhoea and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include fluoxetine, paroxetine, quinidine and terbinafine. In concomitant use with quinidine, plasma concentrations of dextromethorphan have increased up to 20-fold, which has increased the CNS adverse effects of the agent. Amiodarone, flecainide and propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine and thioridazine also have similar effects on the metabolism of dextromethorphan. If concomitant use of CYP2D6 inhibitors and dextromethorphan is necessary, the patient should be monitored and the dextromethorphan dose may need to be reduced.

4.6 Fertility, pregnancy and lactation

Although dextromethorphan has been in widespread use for many years without apparent ill consequence, there is insufficient information on the effects of administration during human pregnancy. In addition, it is not known whether dextromethorphan or its metabolites are excreted in breast milk.

Benylin Non-Drowsy for Dry Cough should therefore only be used when the potential benefit of treatment to the mother exceeds any possible hazards to the developing foetus or suckling infant.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Post-marketing Data:
Adverse drug reactions (ADRs) identified during post-marketing experience with Dextromethorphan are included in table below. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and < 1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000, <1/1,000
Very rare	<1/10,000
Not known	(cannot be estimated from the available data)

Adverse Drug Reactions Identified During Post-Marketing Experience with Dextromethorphan Frequency Category Estimated from Clinical Trials or Epidemiology Studies	
SOC	
<i>Frequency category</i>	Adverse Event Preferred Term
Gastrointestinal Disorders	
<i>Not known</i>	Abdominal pain
<i>Not known</i>	Diarrhoea
<i>Not known</i>	Nausea
<i>Not known</i>	Vomiting
Immune System Disorders	
<i>Not known</i>	Angioedema
<i>Not known</i>	Pruritus
<i>Not known</i>	Rash
<i>Not known</i>	Urticaria
Nervous System Disorders	
<i>Not known</i>	Dizziness
<i>Not known</i>	Psychomotor hyperactivity
<i>Not known</i>	Somnolence
Psychiatric Disorders	
<i>Not known</i>	Insomnia

In rare instances the following adverse events may occur: confusion, bronchoconstriction and dyspnoea.

Reporting of Suspected Adverse Reactions.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of overdose may include:

Eye Disorders

- Mydriasis

Nervous System Disorders

- CNS depression
- CNS excitation
- Nystagmus
- Serotonin syndrome

Respiratory, Thoracic and Mediastinal Disorders

- Respiratory depression

Treatment

Gastric lavage and general supportive measures should be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cough suppressant

ATC code: R05DA09

Dextromethorphan is the dextrorotatory isomer of 3-methoxy-N-methyl-morphinan. It is a synthetic morphine derivative that, in contrast to its levoisomer, has no significant analgesic, respiratory depressant or physical dependency properties at recommended doses.

Dextromethorphan is a cough suppressant and acts centrally on the cough centre in the medulla oblongata to elevate the threshold for coughing.

The onset of antitussive effects are realised within 15 to 30 minutes of oral administration, lasting for approximately 3 to 6 hours.

The major metabolite of dextromethorphan, dextrorphan, binds with high affinity to σ -receptors to produce its antitussive activity without exhibiting the classic opiate effects that occur from binding into μ - and δ -receptors. Dextrorphan also exhibits binding activity at serotonergic receptors and was shown to enhance serotonin activity by inhibiting the reuptake of serotonin.

5.2 Pharmacokinetic properties

Absorption

Dextromethorphan is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations reached in approximately 2 to 2.5 hours. The low plasma levels of dextromethorphan suggest low oral bioavailability secondary to extensive first-pass (presystemic metabolism) in the liver. The maximum clinical effects occur 5 to 6 hours after ingestion of dextromethorphan.

Distribution

Dextromethorphan is widely distributed in the human body. Dextromethorphan and its active metabolite, dextrorphan, are actively taken up and concentrated in brain tissue. It is not known if dextromethorphan or dextrorphan are excreted in breast milk or cross the placenta.

Metabolism

Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation (CYD2D6) is the main determinant of dextromethorphan pharmacokinetics in human volunteers.

It appears that there are distinct phenotypes for this oxidation process resulting in highly variable pharmacokinetics between subjects. Unmetabolised dextromethorphan, together with the three demethylated morphinan metabolites dextrorphan (also known as 3-hydroxy-N-methylmorphinan), 3-hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine.

Dextrorphan, which also has antitussive action, is the main metabolite. In some individuals metabolism proceeds more slowly and unchanged dextromethorphan predominates in the blood and urine.

Excretion

Dextromethorphan is primarily excreted via the kidney as unchanged parent drug and its active metabolite, dextrorphan. Dextrorphan and 3-hydroxy-morphinan are further metabolised by glucuronidation and are eliminated via the kidneys.

The elimination half-life of the parent compound is between 1.4 to 3.9 hours; dextrorphan is between 3.4 to 5.6 hours. The half life of dextromethorphan in poor metabolisers is extremely prolonged, in the range of 45 hours.

5.3 Preclinical safety data

5.3.1. General Toxicology

Acute oral toxicity studies conducted with Dextromethorphan report the following LD₅₀ values (mg/kg): mouse, 210 and rat, 116. Acute subcutaneous toxicity with Dextromethorphan reports the LD₅₀ value (mg/kg): mouse, 112. Acute intravenous toxicity with Dextromethorphan reports the LD₅₀ value (mg/kg): rat, 16.3.

Repeat dose toxicity studies conducted in rats for 13 weeks duration at doses up to 100 mg/kg and 27 weeks at 10 mg/kg, and of 14 weeks in dogs by oral gavage at doses up to 4 mg/kg on five days per week. The only effect recorded was of reduced body weight gain in the rat 13-week study at the highest dose.

5.3.2. Genetic Toxicology

Dextromethorphan hydrobromide was negative in the bacterial reverse mutation assay (Ames test). Dextromethorphan 39 mg/kg is reported to be negative in *in-vivo* mouse micronucleus test and comet assay. Dextromethorphan was reported to be negative in *in vitro* chromosome aberration assay tested up to 200 µg/ml.

5.3.3. Carcinogenicity

There are no known reports of animal carcinogenicity studies for Dextromethorphan. There is no evidence of a carcinogenic risk to humans.

The overall weight of evidence for Dextromethorphan and its structural analogues, supports the conclusion that this class of phenanthrene-based chemicals, and Dextromethorphan, in particular, are not genotoxic *in vitro* or *in vivo*, and do not represent a carcinogenic risk to patients.

5.3.4. Teratogenicity

There was no association between dextromethorphan and malformations, Dextromethorphan is generally considered safe to use during pregnancy.

5.3.5. Fertility

Mating, gestation, fertility, littering and lactation were studied in rats at doses upto 50 mg/kg and no adverse effects were found. There is no evidence of a fertility impairment risk to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Levomenthol
Sodium benzoate (E211)
Sucrose
Glycerol
Liquid glucose
Sorbitol, Liquid (non-crystallising) 70% (E420)
Saccharin sodium
Citric acid monohydrate
Ethanol 96%
Caramel T12
Imitation peach flavour
Carbomer
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C. Keep the bottle tightly closed in order to protect from light and moisture.

6.5 Nature and contents of container

30 ml, 125 ml and 300 ml round amber glass bottles with ROPP aluminium caps or 3 piece child resistant, tamper evident closures fitted with a PE- Alu- PET or polyethylene/expanded polyethylene laminated wad or with a plastic HDPE cap fitted with a PE-Alu-PET wad.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McNeil Healthcare (Ireland) Ltd.
Airton Road
Tallaght
Dublin 24.

8 MARKETING AUTHORISATION NUMBER

PA0823/029/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 November 1994

Date of last renewal: 10 November 2009

10 DATE OF REVISION OF THE TEXT

December 2016